AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 01: Arthritis and Nontraumatic Joint Disease

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Contents

Figures

Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high-impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the four topics for which (1) at least preliminary phase III data were available; (2) information was compiled before September 21, 2012, in this priority area; and (3) we received six to nine sets of comments from experts between March 20, 2012, and October 19, 2012. (Thirty topics in this priority area were being tracked in the system as of October 26, 2012.) Three of the topics emerged as having potential for high impact on the basis of experts' comments and their assessment of potential impact. They are noted by an asterisk in the table below. The material in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 01: Arthritis and Nontraumatic Joint Disease

Topic	High-Impact Potential
1. * Autologous mesenchymal stem cell therapy for osteoarthritis	Moderately high
2. * Autologous platelet-rich plasma therapy for osteoarthritis	Moderately high
3. Canakinumab (Ilaris) for treatment of systemic juvenile idiopathic arthritis	No high-impact potential at this time
4. * Tofacitinib (Xeljanz) for treatment of rheumatoid arthritis	Moderately high

Discussion

The topics that emerged as higher impact were in disease categories of osteoarthritis (OA) and rheumatoid arthritis (RA), conditions in which experts perceived considerable unmet need because of a lack of effective treatments and their impact on quality of life.

Osteoarthritis

OA affects millions of Americans and is expected to affect a greater proportion of the population in the coming decades as more people reach age 65 years and older. OA, the most common form of arthritis, is a chronic condition characterized by the progressive loss of cartilage in one or more joints. As the cartilage that cushions a joint gradually wears away from use, bones rub against each other, causing pain, stiffness, and loss of joint flexibility. Increasing age, obesity,

injury to or overuse of a joint, and genetics can all contribute to the disease. The National Institute of Arthritis and Musculoskeletal and Skin Diseases estimates that almost 27 million Americans have some degree of OA. Current treatments for OA include over-the-counter analgesics and nonsteroidal anti-inflammatory drugs, exercise and/or physical therapy, and weight loss if indicated. More severe cases may warrant corticosteroid or viscosupplementation injections. However these agents have no anabolic or anticatabolic activity on chondrocytes, which are the cells responsible for maintaining cartilage. Two interventions were deemed by experts commenting on them to have potential to disrupt the current OA treatment paradigm because of their potential to regenerate articular cartilage or inhibit OA's degenerative processes. These interventions are not proprietary products, but rather biologic products prepared onsite by the health care facilities delivering the treatment to patients.

Autologous Mesenchymal Stem Cell Therapy for Osteoarthritis

- **Key Facts**: Autologous mesenchymal stem cell (MSC) therapy for OA consists of adult stem cells derived from the patient's own bone marrow, synovium, periosteum, skeletal muscle, or adipose tissue and combined with platelet-rich plasma (PRP) and fat matrix. The preparation is injected into the patient's intra-articular space. The methods used to prepare MSCs have not yet been standardized and differ among health care facilities making and administering the preparations. This may lead to different outcomes among treatment centers. MSCs are purported to lead to cartilage regeneration because of the secretion of growth factors by the cells or from differentiation of MSCs into chondrocytes. The exact mechanism remains unknown. MSCs are purported to have immunomodulatory, antiapoptotic, proliferative, and angiogenic effects on cells in the intra-articular space. The therapy can conceivably be made and delivered by any suitably equipped health care center, and some physicians have begun to offer it. Reported charges for the procedure ranged from $7,000 to $10,000. Our searches of 11 representative, private, third-party payers that publish their coverage policies online showed that all of the payers listing policies for MSC for OA consider the therapy investigational at this time.
- **Key Expert Comments**: Experts stated that effective, minimally invasive OA therapies that can prevent joint replacement surgery are needed, especially because many patients with OA are experiencing symptom onset at an earlier age because of active lifestyles. MSC therapy has the potential to be a first-line OA-treatment option that could regenerate articular cartilage. However, experts were cautiously optimistic about the potential impact of MSC therapy because of the paucity of data demonstrating its ability to relieve symptoms and regenerate cartilage. Additionally, the current lack of third-party payer coverage and high out-of-pocket costs for patients are expected to temper the impact of MSC therapy for treating OA.
- **Potential for High Impact**: Moderately high

Autologous Platelet-Rich Plasma Therapy for Osteoarthritis

- **Key Facts**: Autologous PRP therapy is a processing of the plasma portion of a patient's blood to achieve a higher-than-normal concentration of platelets, which are purported to secrete a wide variety of growth factors and cytokines and may promote tissue regeneration and repair. As such, PRP is thought by some researchers to have potential regenerative effects on cartilage in patients with OA. PRP therapy has been used by high-profile athletes to speed their recovery process after soft-tissue injuries. PRP is injected directly into the intra-articular space, under ultrasound guidance. As with MSC therapy, preparation

protocols and injection frequency vary among treatment centers. The evidence base for PRP lacks sufficiently large, blinded, prospective, randomized controlled trials that compare it to other standard treatments for OA. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 8 payers that have specific policies that deny coverage for the procedure because they consider PRP injections to be experimental or investigational. The cost of PRP therapy has been reported to range from $500 to $1,500 per injection, and a patient may receive more than one injection over time.

- **Key Expert Comments**: Overall, experts were divided on the impact that PRP might have on OA treatment. Similar to the experts' comments on MSC therapy, several experts stated that if PRP were to be proven effective and becomes accepted first-line therapy that regenerates joint cartilage and restores function, its impact would be major on patient outcomes and costs of treating OA. However, more data and clinical experience are needed to standardize preparation procedures and regimens and test those regimens in randomized controlled trials to determine whether the procedure regenerates cartilage, has a durable effect, and reduces the need for additional OA treatment for the affected joint, compared with other standard therapies for OA.
- **Potential for High Impact**: Moderately high

Rheumatoid Arthritis

RA is a chronic inflammatory disease that affects an individual's joints throughout the body and often progresses to permanent joint damage, deformity, and functional disability, so the disease burden is high. In recent years, biologic therapies such as monoclonal antibodies (e.g., infliximab, adalimumab, tocilizumab) and tumor necrosis factor alpha (TNF-alpha) inhibitors (e.g., etanercept) have become standard care for RA that no longer responds to first-line therapy of disease-modifying antirheumatic drugs (DMARDs). Biologics are intended to reduce disease activity, slow joint damage, and improve physical function. However, they require administration by intramuscular, subcutaneous, or intravenous injection and are associated with increased incidence of immunosuppression, resulting in serious infections, including tuberculosis. New RA therapies with improved efficacy, tolerability, and convenience that can effectively control RA symptoms without severe immunosuppression represent a challenging, but significant, unmet need. Expert comments led to designation of one RA therapy in phase III development as having high potential impact.

Tofacitinib (Xeljanz) for Treatment of Rheumatoid Arthritis

- **Key Facts**: Tofacitinib (Xeljanz®, Pfizer, Inc., New York, NY) is an oral, targeted DMARD that the U.S. Food and Drug Administration approved in November 2012 for treating adults with moderately to severely active RA whose symptoms have not responded adequately to, or who are intolerant of, methotrexate. Tofacitinib inhibits one or more Janus kinase (JAK) signaling pathways believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells, production of rheumatic factor, and activation of T cells. By inhibiting JAK pathway(s), tofacitinib may suppress the inflammatory reactions that are the basis of RA. Tofacitinib is indicated for oral administration, 5 mg twice daily. In results of phase III trials, investigators reported that patients treated with tofacitinib demonstrated improvements in signs and symptoms of RA compared with patients given placebo. These results also extended to patients taking methotrexate or whose disease was unresponsive to methotrexate or a TNF inhibitor. Investigators reported that one open-label extension trial demonstrated durable responses as

long as 36 months. The wholesale cost was reported as $2,055 per month for 30 tablets, or about $25,000 annually, a cost comparable to injectable DMARD therapies. Third-party payer policies were not identified as of this writing, but the drug would likely be listed as a specialty pharmaceutical requiring preauthorization.

- **Key Expert Comments**: Overall, experts thought that the drug could address the unmet need for a new, more effective RA therapy with the enhanced convenience of oral administration and lower cost. Experts thought that tofacitinib might also improve health outcomes through earlier diagnosis and treatment in the primary care setting. If so, improvements in access to care might reduce costs and health disparities for these patients. Experts thought that tofacitinib might have more favorable pricing than injectable biologic therapies, but some experts expressed strong concerns regarding its safety and tolerability because of infections reported in the completed trials, which could present a barrier to diffusion.
- **Potential for High Impact**: Moderately high

Osteoarthritis Interventions

Autologous Mesenchymal Stem Cell Therapy for Osteoarthritis

Mesenchymal stem cells (MSCs) are adult stem cells that are involved in maintaining the relative stability of internal physiologic conditions of many tissue types in the body.[1] As progenitor cells, MSCs are purported to retain the ability to differentiate into a number of cell types, including chondrocytes, which are the cells responsible for maintaining cartilage.[2,3] MSCs derived from the patient (autologous) can be isolated and expanded in vitro, providing patient-matched stem cells to treat the large cartilage defects observed in osteoarthritis (OA). However, the mechanism by which these cells lead to cartilage generation is still unclear.[1] MSCs may differentiate into chondrocytes and fill in a cartilage defect. Additionally, MSCs are known to have effects on the intra-articular environment, including immunomodulation, host cell survival, proliferation of endogenous tissue progenitor cells, local angiogenesis, and inhibition of fibrosis.[1] The methods used to prepare MSCs have not yet been standardized; the cells can be isolated from bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue.[2] MSCs isolated from these different tissues are purported to exhibit differences in their ability to proliferate and/or their propensity to differentiate into chondrocytes.[2] To have an adequate number of MSCs for treatment, the cells from a tissue sample must either be concentrated by centrifugation or expanded in vitro.[3,4] The method chosen to acquire adequate cells may also influence the nature of the MSCs used for treatment. Additionally, patient characteristics such as age and the presence of OA have been shown to affect the ability of MSCs to differentiate into chondrocytes.[2,5] Thus, many factors can introduce variability in this procedure. When used, MSCs have also been given with other therapies, including platelet-rich plasma.

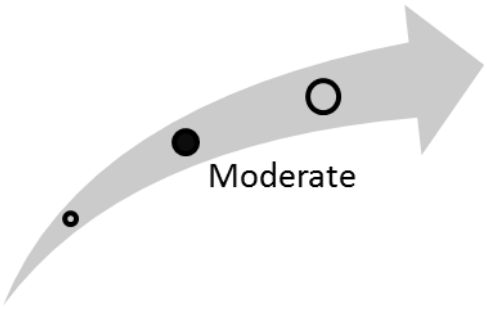
In patients with knee OA and a Kellgren-Lawrence status of II, III, or IV (n=23) who were treated with a combination of autologous MSC (concentrated bone marrow isolate), platelet-rich plasma (PRP), and fat matrix injected into the intra-articular space, improvements in several disease measures were reported for patients at 6-month (n=12) and 12-month (n=10) followup. The investigators reported that patients treated with MSC therapy had improvements in patient pain measured on a visual analog scale (VAS) of 34% and 25% from baseline at 6 and 12 months, respectively. Patient global assessment of disease improved 33% and 33% from baseline at 6 and 12 months, respectively. Physician global assessment improved 51% and 53% from baseline at 6 and 12 months, respectively. Fifty-foot walk pain improved 26% and 17% from baseline at 6 and 12 months, respectively. Western Ontario and McMaster Universities Osteoarthritis Index improved 20% and 8% from baseline at 6 and 12 months, respectively. Ultrasound measurement of patellofemoral cartilage thickness at seven standardized points also revealed that patients treated with MSC had a 0.4 mm and 0.8 mm mean improvement from baseline to 6 months and 12 months, respectively.[4]

Although the efficacy of MSC treatment for OA has not yet been established, the treatment could conceivably be performed at any suitably equipped health care center, and some physicians have begun to offer it as a treatment.[6,7] One center offering MSC therapy quotes a price of about $10,000 for a regimen that involves a single injection of a bone marrow concentrate, PRP, and autologous fat scaffold plus the required pretreatment and posttreatment assessments.[8] Another center offering the treatment reportedly charges from $7,000 to $9,000 for the procedure.[9] Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that 5 list coverage determinations for MSC therapy for OA.[10-14] These five payers stated MSC therapy is investigational because of insufficient evidence or insufficient long-term safety or efficacy outcomes.[10-14]

Clinical Pathway at Point of This Intervention

Patients with OA are often prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, nabumetone, and naproxen as well as the COX-2 inhibitor celecoxib. Physicians can recommend exercise, physical and/or occupational therapy, and weight loss. More severe cases of OA may warrant prescription painkillers, corticosteroid injections, or viscosupplementation. For patients with severe, persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement.[15] MSC therapy is intended to be used as a cartilage-restoring technique in patients with uncontrolled OA pain whose disease is not responding to conservative therapy.

Figure 1. Overall high-impact potential: autologous mesenchymal stem cell therapy for osteoarthritis



Experts commenting on this technique stated that effective, minimally invasive OA therapies that can prevent or delay joint replacement surgery are needed, especially because OA is expected to continue to increase in prevalence, including in younger patients. Autologous MSC has the potential to be the first treatment for OA that could regenerate articular cartilage. However, data regarding the ability of MSC to improve OA symptoms and regenerate cartilage are limited; thus, experts were cautious in their optimism about the potential impact as the evidence base grows. Additionally, the current lack of third-party payer coverage and high out-of-pocket costs for patients are expected to temper the impact of MSC therapy for OA. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.[16-22] Overall, experts stated that current OA therapies treat only the symptoms and do not restore cartilage or joint function. Thus, a significant unmet need exists for treatments that can restore cartilage and obviate or delay the need for joint replacement. Additionally, two experts representing a health systems perspective noted the median age for OA onset has declined, the number of patients with OA has increased, and the number of patients with OA is expected to increase in the next decade, adding to the urgency of addressing this unmet need.

Experts stated that the preliminary data were encouraging, and they were cautiously optimistic about the potential of MSCs to improve patient health outcomes. MSCs could potentially relieve symptoms and regenerate cartilage, providing a novel treatment option to reverse the disease course of OA and reduce the need for additional therapies. Two experts representing a health systems perspective noted that the most positive data described using MSCs combined with PRP and fat matrix, complicating analysis of the effect of MSC therapy alone.

If the procedure is adjunctive to current therapies it could increase health disparities by adding to costs. Some experts agreed that lack of third-party payment for MSC therapy and its implementation in specialty centers are more likely to create health disparities in treating OA.

In general, the experts stated, MSC injection is similar to other injections used to treat OA; however, changes in infrastructure such as equipment and facilities to handle, isolate, and expand MSC in a U.S. Food and Drug Administration (FDA)–compliant manner will be needed in many locations where there may already be demand for the procedure. Allogeneic MSCs are expected by some experts to require less infrastructure expansion by treatment facilities than autologous MSCs.

The experts opined that MSC therapy would be accepted by clinicians if the procedure were to be found safe and effective in larger, randomized clinical trials, because MSC therapy is less invasive than joint replacement surgery. However, an expert representing a health systems perspective stated that regulatory issues and the poorly defined impact of harvesting MSC from different anatomical sites on cellular differentiation and function in the body could reduce clinician acceptance. Clinicians were expected to be more likely to suggest PRP in younger patients with OA who may have an active lifestyle and may want to delay joint replacement surgery. The experts stated that patients with OA pain that does to respond to conventional therapy are likely to accept whatever treatment is recommended by their clinicians. However, the need for bone marrow harvest could be a significant barrier to patient acceptance. Additionally, although some patients may be highly interested in new, effective, nonsurgical treatment for their OA, current lack of reimbursement and high out-of-pocket cost of the procedure, availability of the procedure, and the use of stem cells may serve as barriers to acceptance for some patients.

The experts stated that MSC therapy could reduce the cost of care if the procedure can reduce the need for joint replacement surgery or delay the need for surgery. If favorable cost-effectiveness data become available for MSC therapy, payers may cover the procedure, which could lower costs for patients. One expert representing a research perspective stated that if MSC therapy can be used in earlier stages of the disease and in younger patients and if MSC can prevent disease progression, it could increase patient's ability to exercise and their mental well-being, which could reduce healthcare costs.

Overall, experts were divided on the impact that MSC therapy may play in treating OA. One clinical expert and three other experts representing each of the other perspectives stated that if it becomes the first therapy shown to regenerate joint cartilage and restore function it could be a huge advance in treatment for many patients, allowing them to avoid the cost and complications of joint replacement surgery. Another clinical expert stated that MSC therapy would be used only as an adjunct treatment for patients whose disease is refractory to microfracture surgery. Another expert representing a research perspective stated that MSC could bridge the gap in treatment between pain relief and joint replacement surgery. Finally, an expert representing a health systems perspective stated several treatments for OA are available and this would be viewed as an additional option.

Overall, experts stated that effective OA therapies that can prevent joint replacement surgery are needed. MSC could be the first treatment option for OA that could regenerate cartilage. However, data regarding the ability of MSC to improve OA symptoms and regenerate cartilage are limited; thus, experts were cautiously optimistic about the potential impact of MSC therapy while the evidence base increases.

Autologous Platelet-Rich Plasma Therapy for Osteoarthritis

PRP involves processing a plasma portion of a patient's blood to achieve a higher-than-normal concentration of platelets, which are purported to secrete a wide variety of growth factors and cytokines and may promote tissue regeneration and repair.[23] As such, PRP is thought by some to have potential to address the underlying pathology of OA rather than only ameliorating symptoms of the disease.[24] PRP has been used in a number of hemostatic applications as well as for treating soft-tissue injuries such as tendonitis and chronic wounds.[23] Patient blood is collected and centrifuged to concentrate platelets in a small volume of plasma (about 5 mL) for each injection; clinicians inject it into the patient's intra-articular space under ultrasound guidance.[24-27] Typically, multiple injections are given over the course of several weeks.

In one study, patients with knee OA (n=144) received either three injections of platelet concentrate (n=72) prepared with a single-spinning procedure (PRGF) or three injections of PRP (n=72) obtained with a double-spinning approach. The investigators reported that both treatment groups showed statistically significant improvements in all endpoints and at all time points evaluated. Younger patients with less cartilage degeneration achieved better results in both groups. Similar improvements were observed with both procedures. International Knee Documentation Committee (IKDC) subjective evaluation increased from 45.0±10.1 at baseline to 59.0± 6.2, 61.3± 6.3, and 61.6±16.2 at 2, 6, and 12 months in the PRGF group, respectively. IKDC increased from 42.1±13.5 at baseline to 60.8±16.6, 62.5±19.9, and 59.9±20.0 at 2, 6, and 12 months in the PRP group, respectively. Increases in swelling (p=0.03) and pain reaction (p=0.0005) were observed in patients treated with PRP injections.[28]

In a retrospective analysis, consecutive patients with primary knee OA (n=86) treated with intra-articular PRP injection were compared with similar patients concurrently treated with hyaluronic acid injection (n=21) three times, with 1 week between injections. The mean VAS to measure pain severity at baseline was 8.2 (range 7–10); it was 3.2 (range 1–4) and 2.9 (range 0–4) at 12 and 24 weeks after treatment, respectively. Mean IKDC knee score was 57.5 points (range 32–77) at baseline; it was 77.3 points (range 60–95) and 88.9 points (range 69–98) at 12 and 24 weeks after treatment, respectively. Patients receiving PRP demonstrated significant improvements in VAS and IKDC score measures compared with patients receiving hyaluronic acid injection. Both groups had similar safety profiles.[29]

In a study of patients with knee OA (Outerbridge grades I–IV and symptoms of more than 3 months duration; n=261) who were treated with three intra-articular PRP injections every 2 weeks, 6-month followup showed statistically significant improvements in the PRP group for pain, stiffness, and functional capacity compared with patients given ($p<0.0001$).[30] No adverse events were reported.

In another trial, patients with knee OA (n=100 patients, 115 knees) received three intra-articular PRP injections. Statistically significant improvements in all clinical scores (IKDC form, EQ VAS quality of life score) were reported between the baseline evaluation, the end of the therapy, and between baseline and 6- and 12-month followup ($p<0.0005$). The results declined significantly by and after 12-month followup ($p=0.02$) but were still better than at baseline ($p<0.0005$).[25] By 24-month followup, all evaluated outcomes were significantly lower than those observed at 12-month followup. Better results were obtained in younger patients ($p=0.0001$) and in patients with lower degrees of cartilage degeneration ($p<0.0005$). The median duration of the clinical improvement provided by PRP for knee OA was 9 months.[27]

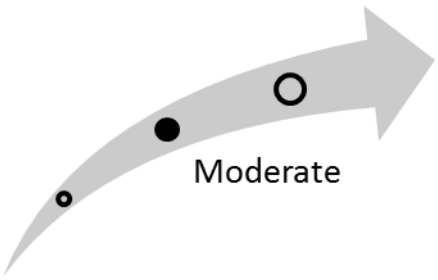
Autologous PRP is not considered a drug or a therapeutic substance by regulatory agencies; therefore, the preparation is not subject to regulatory marketing approval. The patient undergoes

apheresis to collect blood to yield the plasma that is prepared as PRP at a facility (such as a hospital blood bank or blood processing laboratory) according to standard blood processing safety procedures. Thus, the treatment is readily available and may be employed by physicians.[23] Many devices have FDA marketing approval for use in preparing PRP.[25] The therapy cost has been reported to range from $500 to $1,500 per injection.[31] Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 8 payers that have specific policies denying coverage for the procedure because they consider PRP injections to be experimental or investigational.[32-39]

Clinical Pathway at Point of This Intervention

Patients with OA are frequently prescribed NSAIDs such as aspirin, ibuprofen, nabumetone, and naproxen as well as the COX-2 inhibitor celecoxib. Physicians can recommend exercise, physical and/or occupational therapy, and weight loss. More severe cases of OA may warrant prescription painkillers, corticosteroid injections, or viscosupplementation. For patients with severe, persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement.[15] If proven to be effective for treating knee OA, PRP therapy would be employed as a cartilage-restoring technique in patients with uncontrolled OA pain whose disease is not responding to conservative therapy.

Figure 2. Overall high-impact potential: autologous platelet-rich plasma therapy for osteoarthritis



Overall, experts commenting on this intervention were divided on the impact that PRP might have on OA treatment. Treatment options that can restore cartilage and bridge the gap between pain relief and joint replacement are needed. Several experts stated that if PRP were to become standard first-line therapy and actually regenerate joint cartilage and restore function, it would have a large impact on patient outcomes and be a major cost-saving advance in OA treatment. However, more data and clinical experience are needed to demonstrate whether the procedure regenerates cartilage, has a durable effect, and reduces the need for additional OA treatment for the affected joint. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.[40-46] Overall, experts stated that current therapies for OA treat only the symptoms and do not restore cartilage or joint function. Thus, a significant and growing unmet need exists for noninvasive treatments that can restore joint cartilage and function and delay or eliminate the need for joint replacement surgery.

Experts were cautiously optimistic about the potential of PRP therapy to improve patient health outcomes by relieving symptoms, regenerating cartilage, and preventing or delaying joint

replacement surgery. However, some of the experts stated that large, randomized, double-blind trials are needed to better understand PRP's effects on knee and hip OA. One health systems expert stated that data from current trials demonstrate that the effects of PRP could last for only 6–9 months, which suggests PRP only has moderate potential to improve health outcomes. Additionally, experts theorize that PRP provides the most clinical benefit in younger patients, which could affect that impact and diffusion of the intervention.

Two experts with research and systems perspectives stated that the simple, minimally invasive nature of the procedure might enable easy adoption of the procedure in underserved areas. Other experts thought the experimental nature and lack of reimbursement currently associated with the procedure would increase health disparities if the procedure improves outcomes.

Because patients with OA already have the option of treatment delivered by injections in the knee or hip, experts thought, there would be minimal change in infrastructure and patient management by implementing PRP. However, changes in patient management and infrastructure might occur because of fewer joint replacement surgeries, which would cause many inpatient procedures to be handled as outpatient procedures, reducing costs. Additionally, some equipment may need to be purchased for preparing PRP, and staff would need training to handle blood collection and prepare PRP. Because PRP is theorized to be more effective in younger patients, the treatment could alter patient management by promoting earlier detection of OA.

Experts stated that PRP injections could gain broader acceptance if shown to be effective in randomized, double-blind trials and subsequently reimbursed by payers. If the procedure can eliminate the need for joint replacement surgery in some patients, PRP injections are expected to be cost saving. One expert with a health systems perspective stated the some of the available evidence suggests that PRP injections might not have a durable response and that a need for repeated injections could lead to significant long-term costs. One clinical expert also stated that PRP costs were high for a treatment that had only subjective results.

Rheumatoid Arthritis Intervention

Tofacitinib (Xeljanz) for Treatment of Rheumatoid Arthritis

Tofacitinib (Xeljanz®, Pfizer, Inc., New York, NY) is a selective and potent oral tyrosine kinase inhibitor that is being investigated as a targeted disease-modifying antirheumatic drug (DMARD) for treating rheumatoid arthritis (RA). Tofacitinib (formerly tasocitinib) inhibits one or more Janus kinase (JAK) signaling pathways believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells and activation of T cells.[47,48] By inhibiting JAK pathways, tofacitinib could suppress the inflammatory reactions that are the basis of RA.[47,48] Recently approved for marketing, tofacitinib has labeling indicating oral administration, 5 mg twice daily.[48] A targeted therapy that reduces RA-specific inflammatory processes through JAK pathway antagonism could provide better symptom control with fewer adverse events than other DMARD or NSAID-activated anti-inflammatory pathways.

In a phase III, double-blind, 6-month study, adult patients (n=611) with active RA—whose symptoms did not respond adequately to at least one nonbiologic or biologic DMARD and who had discontinued all DMARD therapy except stable doses of antimalarial agents (NSAIDs and glucocorticoid treatment were permitted)—were given tofacitinib or placebo. Different dosing regimens used were 5 or 10 mg twice daily or placebo for 3 months followed by tofacitinib either 5 or 10 mg twice daily. At month 3, more patients given tofacitinib (59.8% and 65.7% in the 5 and 10 mg groups, respectively) met the American College of Rheumatology 20% improvement criteria (ACR20) compared with patients given placebo (26.7% in the combined placebo groups, $p<0.001$ for both comparisons).[49] Disability score reductions from baseline were greater in the 5 and 10 mg groups (-0.50 and -0.57 points, respectively) than in the placebo groups (-0.19 points; $p<0.001$).[49] The tofacitinib 5 or 10 mg twice daily groups did not achieve a significant reduction in the percentage of patients achieving disease activity score lower than 2.6 compared with patients given placebo (5.6% and 8.7% in the 5 and 10 mg groups, respectively, and 4.4% with placebo; $p=0.62$ and $p=0.10$ for the two comparisons).[49]

In another trial (n=1,070), twice daily tofacitinib (5 or 10 mg) or placebo was given alone or with methotrexate. Researchers reported, "ACR response rates showed a trend for improvement over time (month 1-24) with similar ACR20 response rates in tofacitinib monotherapy and tofacitinib on background methotrexate groups at month 24."[50]

In a year-long, phase III trial, patients with moderate to severe, active RA (n=717) with an inadequate response to methotrexate were given tofacitinib 5 or 10 mg twice daily, adalimumab (Humira®) 40 mg injected every other week, or placebo added to a stable methotrexate background. At 3 months, patients taking placebo who were not responding were given tofacitinib. At 6 months, all placebo-assigned patients were given tofacitinib. At 6 months, investigators reported that ACR 20 response rates were higher among patients given tofacitinib 5 or 10 mg twice daily (51.5% and 52.6%, respectively) and among patients given adalimumab (47.2%) than among those receiving placebo (28.3%, $p<0.001$ for all comparisons). Greater reductions in the disability score (called HAQ-DI) were observed at month 3 in the active treatment group than placebo group; at month 6, higher percentages of patients given active treatment had a disease activity score below 2.6 patients than patients given placebo.[51]

In a 6-month, phase III trial, patients (n=399) with moderate to severe, active RA who had an inadequate response to at least one tumor necrosis factor (TNF) inhibitor were given tofacitinib 5 or 10 mg twice a day or placebo and methotrexate. Patients given placebo were given tofacitinib at 3 months. After 3 months of treatment, patients receiving tofacitinib showed a statistically significant reduction in RA signs and symptoms and improved physical function and remission rates, investigators reported.[52]

In a 12-month study of patients with moderate to severe, active RA who had an inadequate response to methotrexate (n=797), tofacitinib 10 mg twice daily met all primary efficacy endpoints. Statistically significant reductions in the signs and symptoms of RA, (measured by ACR20 response rate at 6 months), progression of structural damage (measured by mean change from baseline in modified Total Sharp Score at 6 months), disease activity (measured by rates of DAS28-4(ESR) <2.6 at 6 months), as well as improved physical function (measured by mean change in HAQ-DI at 3 months) were reported, compared with patients treated with placebo.[53]

Finally, an open-label, extension trial of patients with active RA (n=3,227) enrolled in phase II/III trials who were treated with tofacitinib 5 or 10 mg twice daily revealed durable ACR 20, 50, and 70 responses (measuring 20%, 50%, and 70% improvement criteria) at 36 months (72.7%, 52.3%, and 35.2%, respectively).[54]

The most commonly reported adverse reactions during the first 3 months of tofacitinib therapy in trials (i.e., reported by 2% or more of patients receiving tofacitinib alone or in combination with DMARDs) were upper respiratory tract infections (4.5%), headache (4.3%), diarrhea (4.0%), and nasopharyngitis (3.8%).[48] Tofacitinib could cause immunosuppression and has a black box warning about serious infections leading to hospitalization and death as well as lymphoma and other malignancy. Also, Epstein Barr virus-associated posttransplant lymphoproliferative disorder was observed in patients who had renal transplant and were taking concomitant immunosuppressive therapy.[48]

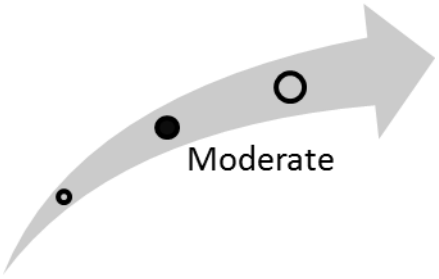
In November 2012, FDA approved tofacitinib to treat adults with moderately to severely active RA whose symptoms have not responded adequately to, or who are intolerant of, methotrexate.[55]

According to one recent estimate, the wholesale acquisition cost of tofacitinib is expected to be about $2,055 per month, about a 7% discount compared with injectable therapies.[56] As of this writing, third-party payer policies had not yet been published, but they are likely to include the drug on their specialty pharmaceutical formularies requiring prior authorization.

Clinical Pathway at Point of This Intervention

Newly diagnosed RA is generally treated with a combination of DMARDs and anti-inflammatory drugs such as NSAIDs and COX-2 inhibitors. For patients in whom combination therapy is not indicated, monotherapy with DMARDs is used. When satisfactory disease control is reached, the DMARD dosage is gradually reduced to minimum levels needed to maintain control of the disease. Flares are treated by increasing DMARD dosages and administering short-term glucocorticoid therapy. Repeated failure of DMARD therapy is typically followed by biologic therapy targeting TNF-alpha. After long-term RA treatment, joint replacement surgery may be suggested for some patients whose RA has not responded to optimal medical management.[57,58] Investigators have not found a cure for RA, and tofacitinib is a targeted DMARD intended to be a potential long-term solution because it appears to play several roles in interfering with progression of RA and has convenient, oral, twice-daily dosing.

Figure 3. Overall high-impact potential: tofacitinib (Xeljanz) for treatment of rheumatoid arthritis



Overall, experts commenting on this intervention thought that tofacitinib might address the unmet need for a new, effective RA therapy with the enhanced convenience and potentially lower cost of oral administration. The experts thought that tofacitinib could improve health outcomes in patients with RA and might lead to health promotion via earlier diagnosis and treatment in the primary care setting. These improvements in access to care could also reduce cost and reduce health disparities. Tofacitinib might have more favorable pricing than injectable biologic therapies (which is yet to be confirmed), but some of the experts expressed strong concerns regarding its safety and tolerability. These safety concerns could present significant barriers to diffusion. Data from ongoing larger trials will continue to define the potential role of tofacitinib in improving health outcomes in patients with RA. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[59-64] Overall, the experts generally concurred that many of the current therapies for RA are expensive and are injectables that only slow disease progression and can induce severe immunosuppression, thus presenting a significant unmet need for new, effective, oral therapies that can minimize RA symptoms with fewer side effects, better tolerability, and lower cost.

The experts agreed that the underlying theory behind tofacitinib action is sound, providing a new targeted mechanism of action for immunoregulation. The experts were optimistic about the potential of tofacitinib to reduce signs and symptoms of RA, although they had concerns regarding the adverse events associated with tofacitinib use. However, one expert representing a clinical perspective stated that some patients who could benefit from biologic therapy perceive injectables as having more adverse events; all things being equal these patients could be responsive to tofacitinib therapy.

Some experts stated that tofacitinib might reduce health disparities by reducing the need for access or travel to infusion centers. Tofacitinib could also increase access to care if primary care physicians were comfortable prescribing tofacitinib; however, one clinical expert stated that this is unlikely because primary care physicians are typically already uncomfortable prescribing methotrexate. Disparities could also be reduced if the drug were lower in cost than biologic therapy, which the experts were also unsure would occur.

In general, the experts thought that tofacitinib would not shift how RA is treated or managed. Experts thought that as an oral agent, tofacitinib might become the preferred treatment in cases in which conventional DMARDs fail or could be used in combination with DMARDs but before the use of injectable biologics, thus shifting the treatment model. One clinical expert also stated that tofacitinib could shift the care setting for RA from the specialist office to primary care offices,

which might allow for earlier treatment but could lead to inappropriate treatment by reducing access to a specialist.

Experts all thought tofacitinib would have a large impact on costs, but diverged in how the impact would play out. Some experts stated that tofacitinib would increase costs because, as a new agent, it would be used adjunctively. Other experts commented that the drug would supplant costly injectable biologics and thus, would save costs. At the time during which the experts commented, tofacitinib had not yet received marketing approval. A clinical expert stated that it was rumored that Pfizer would set tofacitinib costs at about two-thirds the cost of the biologics. Experts thought that many patients and physicians would be eager to try tofacitinib if it could eliminate injections with biologics. However, adverse events observed in clinical trials completed to date, such as infections, increases in cholesterol levels, and liver damage in some patients, were also cited as potential barriers to acceptance and potential sources of controversy. One clinical expert stated that the adverse-event profile might lower acceptance of tofacitinib by primary care physicians, but not rheumatologists who are very excited about having an additional treatment option.

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